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Local Resection and Brachytherapy Confined to the Lumpectomy Site for Early Breast Cancer: A Pilot Study

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Background and Objectives: The commonest site of local breast recurrence after breast conservation surgery is the primary tumor bed. We have tested the feasibility of outpatient high dose rate brachytherapy to the primary tumor bed as the only radiation. Our technique relies on the placement of surgical clips to mark the tumor bed.

Methods: Between March 1992 and January 1996, 39 patients with clinical T1 T2 breast cancer were enrolled in this pilot study. The first 13 patients had intraoperative implantation of the breast. The remaining 26 patients had outpatient postoperative implantation under general anesthesia (2 patients) or local anaesthesia (24 patients). High dose rate brachytherapy was given twice daily at least 6 hours apart for a total dose of 37.2 Gy in 10 fractions over 5–7 days.

Results: Three patients had mild clinical cellulitis responding to oral antibiotics. One patient had a small sinus in the lumpectomy scar requiring local excision to heal. Four patients developed fat necrosis at the lumpectomy site at 4 (1 patient), 13 (1 patient), and 18 months (2 patients) post radiotherapy. Patient rated satisfaction with treatment was high. At a median followup of 20 months, one infield local recurrence has been salvaged by wider resection and postoperative conventional external beam radiation.

Conclusions: Except for fat necrosis, which may be associated with this technique, complications have been minimal. Outpatient implantation under local anesthesia is feasible. Longer followup is required to establish the local control rates. *J. Surg. Oncol. 1997;65:263–268.*

KEY WORDS: high dose rate; fat; necrosis

INTRODUCTION

After conservative breast surgery for early breast cancer, it is standard practice to radiate the entire breast. It is not known whether or not this is the optimum radiotherapy volume for all patients with T1 or T2 breast cancer. The Christie Hospital breast conservation trial [1,2] showed a 15% actuarial breast recurrence rate for local field radiation vs. 11% for wide field radiation for infiltrating ductal carcinomas 4 cm or smaller. Breast recurrence rates were much higher with local field radiation for invasive lobular cancers (34%). The authors con-

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cluded that limited field radiotherapy is feasible, but recommended improved selection criteria and treatment technique.

It is difficult to identify a subgroup of women who could be spared radiation after conservative breast surgery for invasive breast cancer [3]. Even in highly selected patients with early-stage breast cancer managed by surgery alone, a 16% risk of first failure in the breast has been reported [4]. Breast radiation continues to be an important adjuvant treatment for breast cancer.

We have performed a pilot study of local brachytherapy to the lumpectomy site only of women who have had conservative breast surgery for invasive breast cancer. This approach is a much shorter, potentially less expensive alternative to conventional external beam radiation. This report describes our preliminary results, including complications and patient acceptance.

MATERIALS AND METHODS

Between March 1992 and January 1996, 39 patients were accrued to a pilot study of high dose rate brachytherapy as the only radiation after conservative breast surgery. Eligibility criteria were: clinical T1 and T2 breast cancer by clinical examination or mammography and negative regional nodes by clinical examination; the lumpectomy site had to be implantable using direct, intraoperative visualization, or postoperative localization of surgical clips marking the tumor bed; the microscopic resection margins had to be negative for invasive and in situ breast cancer. Patients with an extensive intraductal component were eligible, but patients with predominantly invasive lobular histology were excluded. The protocol was approved by the local ethics review board and informed consent obtained from all patients.

At the time of lumpectomy or wider excision, clips were placed to mark the deep, the superior, the lateral, and the medial walls of the cavity. The lumpectomy site was closed using only subcuticular absorbable sutures. Perioperative antibiotics or surgical drains for the lumpectomy site were not used. Separate lumpectomy and axillary dissection scars were used in 36 patients. The primary tumor was removed with at least 1 cm grossly normal margins.

The technique of tumor bed localization and implantation has been previously described [5]. For intraoperative implantation, the surgeon, radiation oncologist, and physicist were present. Stainless steel trocar needles of 1.5 mm outer diameters and lengths up to 20 cm were implanted from lateral to medial using plastic templates as a guide. The most cephalad and the most caudad needles in the deep implant plane were placed first. The lumpectomy site was then closed, after which the remaining needles are placed. This sequence avoids tension on the surgical scar that would result from placing all needles with the cavity open.

For postoperative implantation under local anesthesia, topical anesthetic cream was applied to the surface of the breast 1½–2 hours prior to implantation. The patient received a sublingual sedative 30 minutes before the procedure. Implantation was performed under sterile conditions in the outpatient operating room. Local 1% or 2% lidocaine was infiltrated into the planned needle tracks, which have been premarked on the breast. Usually, 2–3 ml of lidocaine were used per track; additional lidocaine was used if the patient still had discomfort during the procedure.

After intraoperative implantation, the lumpectomy sites were allowed to heal for at least 48 hours before radiation. Postoperative implantation was done an average of 9 weeks after breast surgery; radiation started the next day. Initially, patients were treated over five consecutive days. Later, the weekend break was permitted if necessary.

Brachytherapy was given using the high dose rate remote afterloading microselectron (Nucletron, Nucletron Trading, B.V., Lersum, The Netherlands). The patients were treated twice a day with each treatment at least 6 hours apart. Each patient received a total of 10 fractions over 5–7 days. The total dose was 37.2 Gy prescribed as a minimum peripheral dose encompassing the target volume.

Patients implanted postoperatively received radiation as outpatients. Needles were removed from the lateral side of the breast, after the last fraction of brachytherapy, using sterile technique. A sterile, dry dressing was kept on the breast for 2–3 days before the patient was allowed to wash the area.

Adjuvant tamoxifen or chemotherapy was prescribed according to our breast multidisciplinary team guidelines. Axillary node positive patients received tamoxifen if they were postmenopausal with positive estrogen and/or progesterone receptors; otherwise, they received chemotherapy. Initially, axillary node negative, receptor positive patients received tamoxifen for tumors >2 cm. This guideline was revised in May 1995 to treat patients with tumors >1 cm. Axillary node negative, receptor negative patients received adjuvant chemotherapy if they were 65 years or younger and had poorly differentiated tumors >2 cm. This guideline was also revised in May 1995 to include patients with tumors >1 cm and with lymphovascular invasion or high histologic grade.

Patients were followed weekly for 4–6 weeks after radiation to assess local side effects and healing. Further followup was every 3 months alternating between the surgeon and the radiation oncologist. Every 6 months, the patient and the radiation oncologist completed subjective and objective questionnaires, respectively, assessing the cosmetic outcome. Color slides of the treated

breast were taken by a photographer from the visual services department at 1–2 weeks after treatment and at 1 year and 3 years. Follow-up mammograms were done 6 months posttreatment and then yearly.

Acute toxicity from treatment was scored using World Health Organization (WHO) criteria [6]. Patient discomfort during implantation under local anesthesia was graded as none, mild (no additional anesthetic required), moderate (additional anesthetic required), or severe (pain despite additional local anesthetic).

RESULTS

Thirty-nine of 74 eligible patients consented and completed the study treatment for an acceptance rate of 52.7%. The median age of the 39 women was 59 years (range 39–84 years). Twenty-one cancers occurred in the right breast and 18 in the left breast. The average tumor size was 15.6 mm (range 4–45 mm). Thirty-five cancers were infiltrating mammary cancers and the others were tubular (1), mucinous (1), medullary (1), and carcinosarcoma (1).

Six patients had intraoperative implantation (Group A). Seven patients had implantation after definitive breast surgery and at the time of axillary dissection (Group B). Twenty-six patients had outpatient implantation after all surgery (Group C); the first two were done under general anesthesia and the others (24) under local anesthesia.

The average number of needles implanted per patient was 7 (range 3–11). There were 11 single plane implants, 25 double plane, and 3 triple plane implants.

An acute skin reaction from radiation developed in 21 of 39 patients (53.8%). The skin reaction was always very localized to skin immediately over the target volume and developed in all cases within the first 1–2 weeks postradiation. It was grade 1 in 15 patients, grade 2 in 5 patients, and grade 3 in 1 patient. Three patients had mild clinical cellulitis during radiation, and all cleared with oral antibiotics. Only 1 of the 3 patients had intraoperative implantation. One patient, who received epirubicin containing chemotherapy starting 4 weeks after brachytherapy for an upper inner quadrant carcinosarcoma, had a small sinus in the lumpectomy scar that required local excision to heal.

Among the 24 patients who had outpatient implantation under local anesthesia, discomfort was nil in 11 patients, mild in 6, and moderate in seven. Patients gave the overall cosmetic result of treatment an average score of 81.9% at 6 months and 78.5% at 12 months (range 50–100%), 100% being excellent cosmesis. Patient scores for satisfaction with treatment averaged 91.6% at 6 months and 90% at 12 months (range 50–100%). A more detailed analysis of cosmesis will be reported separately, after longer followup.

Four patients developed clinical fat necrosis at 4 (1 patient), 13 (1 patient), and 18 (2 patients) months postradiotherapy. All were confirmed by biopsy. Fat necrosis presented as a soft, pliable, and lobulated mass in 1 patient (4 months), as a hard nodule in 1 patient (18 months), and as an area of mild to moderate fibrosis in 2 patients (13 and 18 months). In the first patient (4 months), the mammogram also was reported as showing fat necrosis. The mass became firmer over time with excision being done at 30 months postradiation. The other three patients also had surgical resection with no evidence of malignancy, but with histologic fat necrosis. All patients were asymptomatic with no pain related to fat necrosis. A fifth, asymptomatic patient decided to have prophylactic bilateral mastectomies at 18 months posttreatment. Pathology showed fat necrosis at the lumpectomy site with no evidence of malignancy. Two of the four patients with clinical fat necrosis had intraoperative implantation (Group A) with radiation starting 3–4 days later. The other two patients had postoperative implantation (Group C).

At a median followup of 20 months, there has been one infield recurrence at the lumpectomy site. This patient had an upper outer quadrant 15 mm infiltrating mammary carcinoma of high histologic grade with a focus of comedo duct carcinoma in situ. The patient had a postoperative double plane implant. She presented at 20 months posttreatment with normal mammograms and a palpable 15 mm nodule within 20 mm of the lumpectomy scar. The patient was managed with initial local excision followed by wider resection and postoperative conventional external beam radiation to the whole breast to 50 Gy and a 10 Gy boost to the tumor bed. Interestingly, there was no fat necrosis in the local excision specimen, but extensive fat necrosis in the wider resection specimen removed 5 weeks later.

DISCUSSION

Analyses of local failure after conservative breast surgery and breast radiation indicate that most local failures within the first 5 years of followup occur in the primary tumor bed [7–13]. Beyond 5 years, some studies [9,11,13], but not all [8], report an increasing proportion of breast recurrences to occur in a separate quadrant from the original tumor bed. The 8-year results of the Christie trial suggest that this multicentric pattern of recurrence is more likely for invasive lobular tumors than for infiltrating ductal carcinoma [1]. In addition, partial breast irradiation may be as effective as whole breast radiation for infiltrating ductal carcinoma [1,2].

Partial breast radiation using HDR brachytherapy is attractive because of the short course of treatment. We have developed a protocol that reduces the risk of a geographic miss of the tumor bed, an aspect that is critical in

limited field radiation [14]. The implantation and radiation are now both outpatient procedures, maximizing the use of resources. A disadvantage is the increased quality assurance required to deliver this type of treatment. Also, most patients who refused brachytherapy in our study reported the fear of the procedure (''needles'') as their main objection. Using anthropomorphic phantoms to compare localized radiation with electrons versus interstitial implants, Denham et al. [15] concluded that the physical dose distributions favored brachytherapy.

Unlike other pilot studies of limited field radiation, we have accurately defined our target volume using CT planning of the clipped lumpectomy site. Although this smaller volume will limit complications, the optimal target volume is not established. Using low dose rate iridium 192 implants to 55 Gy over 5.5 days, Fentiman et al. [16] reported four cases of wound infection (14.8%) and two cases of skin necrosis (7.4%) at a median follow-up of 27 months. No fibrosis or fat necrosis were reported at a median follow-up of 6 years [17]. Whereas there were 10 breast recurrences (37%) at 6 years median follow-up, 15 of 27 (55.6%) patients had initial positive margins at study entry [17]. Nine of the 10 recurrences were infield. Bolton et al. [18] described two cases of cellulitis and one case of radiation myositis in 22 patients treated with low dose rate iridium-192 to 45 Gy or high dose rate (HDR) brachytherapy to 32 Gy. There were no recurrences at a median follow-up of 8 months. At a median follow-up of 27 months, Cionini et al. [19] documented four breast recurrences in 90 patients (4.4%) treated by quadrantectomy and low dose rate brachytherapy; complications were not stated.

Fat necrosis following whole breast external beam radiation after conservative breast surgery has not been a commonly reported complication [20–24]. Boyages et al. [20] described a 4.5% incidence of fat necrosis or fibrosis requiring surgery after external beam radiation and Iridium-192 implants as boosts in 131 patients. In the Christie trial, 10 (2.8%) cases of fat necrosis were observed after local field external electron beam radiation to the lumpectomy site. The given dose was 42.5 Gy in eight fractions over 2 weeks [2]. In our study, there have been four cases (10.3%) of clinical fat necrosis after HDR brachytherapy, despite the smaller definition of the target volume than that described by Fentiman et al. [17]. A more detailed analysis of the possible factors contributing to fat necrosis in our study will require assessment of dose-volume histograms. It is possible that we have a lower threshold for biopsy in these patients because of our awareness of fat necrosis as a complication (surveillance bias) after radiotherapy. In addition, it is more likely that postradiation changes after localized brachytherapy are more sharply defined from the adjacent unirradiated breast tissue than postradiation changes after whole breast radiation, making detection easier. Finally, of 11 patients who had wider resection after local excision of breast cancer at initial diagnosis, six patients had histologic fat necrosis at the surgical site. The relative contribution of surgical trauma to subsequent clinical fat necrosis after radiation is not known.

In this pilot study, patient-rated cosmetic scores were 80% or higher in 61% of women at 12 months. Patient-rated satisfaction scores with the results of treatment were 80% or higher in 87.5% of women. Liljegren et al. [25] reported good to excellent cosmetic results in 84–90% of patients as rated by the patients themselves after sector resection and conventional external beam radiotherapy to 54 Gy. Although long-term cosmetic results for our pilot study are pending, the early results compare favorably with the patient-rated cosmesis after external beam radiation in that study.

If recurrences after radiation to the lumpectomy site only are detected early, it is possible that wider resection followed by conventional external beam radiation remains an option. No unexpected increase in acute side effects was seen in the only patient with recurrence managed in this fashion in our study.

Longer follow-up is required to establish our local control rates with brachytherapy to the lumpectomy site as the only radiation after conservative breast surgery. This is especially in view of the high recurrence rate reported by Fentiman et al. [17].

CONCLUSIONS

Brachytherapy as the only radiation to the lumpectomy site is feasible based on the low incidence of grade 3 or 4 complications and the preliminary good to excellent cosmetic results. Fat necrosis may be associated with HDR brachytherapy. Longer follow-up is required to establish the local control rates from this investigational treatment.

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COMMENTARY

In the preceding article by Perera and associates, evidence is provided that small breast cancers may be treated exclusively with local radiotherapy to the excision site. In this pilot trial, 39 patients with T1/2 lesions underwent high dose rate (HDR) brachytherapy of 37.2 Gy in 10 fractions over 5–7 days. A single breast recurrence was noted with 20 months median followup.

Although whole breast radiation is standard therapy after lumpectomy and axillary dissection, we certainly must better define in which patients the radiotherapy or axillary dissection may safely be omitted. Several trials are ongoing that seek to answer these questions. What is not apparent from the breast cancer literature to date is whether there is a ''middle ground'' of patients who require radiotherapy postlumpectomy, but only to the local site.

I suspect not. It has been known for decades that lumpectomy, even with negative margins, is not by itself an extirpatory procedure. Rosen [1] and Holland [2] have elegantly shown that there may be a significant amount of disease left behind in the breast after lumpectomy. The clinical correlate of this is markedly evident in the results of NSABP B-06 [3], where the local recurrence rate after lumpectomy alone was 35% at 12 years, compared to 10% after lumpectomy and radiotherapy.

Not surprisingly, the available data on local-field radiotherapy after lumpectomy reveal the same trend. Table I summarizes trials investigating such therapy. Local control rates vary widely depending on the size of lesions, the extent of surgery, and the presence of positive margins; however, they are generally high. The conclusion of the Guy's Hospital investigators is that ''a continuous iridium^{192} implant delivering 55 Gy in 5 days is not an effective means of achieving local control'' [4]. Further, in a randomized trial against whole breast radiotherapy [5], a significantly higher number of local failures were noted in the limited field radiotherapy cohort (19.6% vs. 11% at 7 years).

Patient selection will contribute to better local control with limited therapy in breast cancer. Perera and colleagues may have identified patients for whom local radiotherapy after lumpectomy contributes to similar local control rates as whole breast radiotherapy, although their results are not yet mature. The next step is to determine if these patients may forego radiotherapy entirely to fully optimize their treatment.

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TABLE I. Local-Field Radiotherapy Alone After Lumpectomy for Breast Cancer

Authors[a]	n[b]	Mean lesion size (cm)[c]	% Neg[d] margins	Local therapy (Gy)[e]	Dose rate[f]	Source[g]	Adjuvant chemo/hormones[h]	Recurrence rate	F/U (med)[i]
Cionini et al. [6]	90	T1	92%	mean 58.4	LDR	Ir^{192}	NS	4.4% crude	27 m
Ribeiro et al. [5]	353	T1	81%	40–42.5	N/A	electrons	None	19.6%[j]	65 m
Bolton et al. [7]	22	1.5	100%	45 (11 pt)	LDR	Ir^{192}	AC (4 pts)+	0	8 m
				32 (11 pt)	HDR	NS	Tamoxifen (4 pt)		
Fentiman et al. [4]	27	3.2	37%	55	LDR	Ir^{192}	NS	37% crude	72 m
Perera et al.	39	1.6	NS	37.2 bid	HDR	Ir^{192}	NS	2.6% crude	20 m

[a]Reference number in brackets.
[b]Number of patients.
[c]T1 = lesions ⩽ 2 cm.
[d]Neg = negative.
[e]Gy = Gray; bid = Twice-daily radiotherapy.
[f]LDR = low dose rate; N/A = not available; HDR = high dose rate.
[g]Ir^{192} = Iridium^{192}.
[h]NS = information not stated.
[i]F/U = followup; med = median.
[j]7-year actuarial figure.
pt = patients.

*The opinions and assertions contained herein are those of the author and are not to be construed as official or representing the views of the United States Navy or Department of Defense.

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